Computational Modelling of Nonlinear Calcium Waves

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Abstract

The calcium transport in biological systems is modelled as a reaction-diffusion process. Nonlinear calcium waves are then simulated using a stochastic cellular automaton whose rules are derived from the corresponding coupled partial differential equations. Numerical simulations show self-organized criticality in the complex calcium waves and patterns. Both the stochastic cellular automaton approach and the equation-based simulations can predict the characteristics of calcium waves and complex pattern formation. The implication of locality of calcium distribution with positional information in biological systems is also discussed.

Keywords: calcium transport, stochastic cellular automata, complex system, nonlinear waves, pattern formation, self-organized criticality.

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1 Introduction

Many processes in living organisms such as muscle mechanics, cardiac electrophysiology, adaptation in photo-receptors, and cytoplasm functions involve the calcium ion transport and its physiological functions[1-6]. However, the exact function of Ca^{2+} oscillations and transport is only partially understood although it is believed that they involve in the intracellular communications and synchronization in the response to a local stimulus [13-15]. Even in the simplest one-dimensional case, the proper modelling requires many simplifications and assumptions. The nonlinearity and cross-coupling in the transport mechanisms usually lead to intractable governing equations. Even with certain approximations and simplicity, the mathematical models still lead to nonlinear reaction-diffusion equations if the essence of the calcium ion activities is included.

Nonlinear reaction-diffusion systems can exhibit complex pattern formation [9-12]. The nonlinear system can be simulated using finite difference or finite element methods, or the alternative cellular automata [16]. However, existing implicit numerical solution schemes are not always robust under general boundary conditions. Most of the earlier work have mainly concerned the one-dimensional case with piecewise linear models [10]. Meanwhile, the cellular automata [17,18] have successfully modelled reaction-diffusion systems [16] with relative stable pattern formation. This provides a possibility of dealing with the difficult nonlinear problem of calcium oscillation and waves using finite-state cellular automata with rules derived from related partial differential equations.

On the other hand, self-organized criticality has been found in many systems in nature [7,8] since its discovery by Bak [7] and his colleagues. Since calcium oscillation and waves a very complicated phenomenon with the characteristics of nonlinear reaction-diffusion systems, it can be expected that regular patterns under certain conditions. One natural question related to this is: Do the self-organized criticality exist in the complexity of the calcium transport? However, this is no existing literature addressing this question in the context of calcium transport. This is partly because the

research on calcium activities and their mathematical modelling for biological and physiological processes is still at a very earlier stage [10,14-15].

This paper therefore first extends the existing mathematical models for nonlinear Ca^{2+} waves. Then, a new stochastic finite-state cellular automaton is then formulated to simulate the general nonlinear calcium transport process and pattern formation. Based on the reaction-diffusion equations, the stochastic CA will be formulated. The pattern formation of calcium ions with realistic parameters will be studied. The self-organized criticality will be tested in the complex patterns of calcium concentration. The positional pattern formation and its implication will briefly be discussed.

2 Mathematical Model

2.1 Governing Equations for Calcium Transport

In many physiological processes within cells, Ca^{2+} plays an essential role in controlling cellular behavior and functioning in the sense that calcium ions act as a signalling agent for a wide range of cellular activities. Calcium signaling is mediated through oscillation in intracellular Ca^{2+} concentration. Calcium ions can bind to a vast number of proteins and enzymes, and the binding can initiate a series of reactions that ends in the formation of a chemical called inositol 1,4,5-trisphosphate (IP_3). The diffusion of Ca^{2+} and IP_3 through the cell cytosol can induce further release of calcium ions from stores in the endoplasmic reticulum (ER) through IP_3-sensitive channels. These channels are sensitive to calcium itself, with fast activation for lower concentrations and comparatively slower inhibition, thus leading to the calcium-induced calcium release (CICR). Complex wave characteristics such as plane waves and spiral waves have been observed in experimental studies using *Xenopus* oocytes as pointed out by McKenzie and Sneyd [19]. However, the detail mechanisms underlying these oscillation and waves are only partially understood.

There are several mathematical models for Ca^{2+} wave propagation in the literature, and these include the important models such as DeYoung and Keizer [2], Goldbeter *et al.* [20], Sneyd *et al.* [15] and McKenzie and Sneyd [19]. However, different cell types can results in different mathematical models, although the fundamentals are quite similar. The nonlinearity in the mathematical models can lead to complex pattern formations and spiral waves [21-24]. The model we will use in this paper is an extended version of a two-pool process. In the two-pool model, the calcium Ca^{2+} concentration in the cytoplasm and the concentration in the Ca^{2+}-sensitive pool satisfy the two-pool model [1]. Although it can reproduce the oscillations and waves observed in Xenopus oocytes and generating spiral waves in the higher dimensional situations. The parameters for our simulations are based on the models developed by Atri et al [1] and McKenzie and Sneyd [19]. The functioning of IP_3 in the oscillation and waves has been reviewed in details by Sneyd *et al.* [25], and th calcium signaling has been reviewed by Falcke [26].

We use the variable $u(x, y, t) = [Ca^{2+}]$ for the concentration (μM) of calcium, $v(x, y, t)$ for the fraction of the IP_3 receptors that are active. The variable $p = [IP_3]$ can be treated as a bifurcation parameter for the reason discussed later. Then, the nonlinear model equations for calcium transport [10,13-15] can be written as

$$\frac{\partial u}{\partial t} = D_u \nabla^2 u + J_f - J_p + J_l, \tag{1}$$

$$\lambda \frac{\partial v}{\partial t} = D_v \nabla^2 v + g(u, v), \tag{2}$$

where J_f models the flux of calcium through the IP_3 receptor. J_p models the amount the Ca^{2+} being pumped out of the cytoplasm back into the endoplasmic reticulum or out through the plasma membrane. J_l models the calcium leaking into the cell. We have

$$J_f = kv[\delta + \frac{(1-\delta)u}{k_1 + u}]\varepsilon(p), \quad J_p = \frac{\gamma u^d}{k_u^d + u^d}, \tag{3}$$

$$J_l = \alpha, \quad g(u, v) = \frac{k_3^m}{k_3^m + u^m} - v, \tag{4}$$

and

$$\varepsilon(p) = \frac{p^n}{k_2^n + p^n}, \tag{5}$$

where k_1, k_2, k_3, k_u are constants and α, β, δ are parameters. In addition, $D_v = 0$ is used in most existing models since most models base on the assumption that Ca^{2+} instantaneously activates the IP_3 receptor.

As the number of IP_3 receptors remains approximately constant, thus we may assume that p is fixed and subsequently it can be considered as a bifurcation parameter. In fact, some studies using $p \in [0.24, 0.2434]$ obtained very interesting results [22]. The function $\varepsilon(p)$ is the fraction of IP_3 receptors that have bound IP_3 and increases as p increases. Then, the complete nonlinear model equations become

$$\frac{\partial u}{\partial t} = D_u \nabla^2 u + kw[\delta + \frac{(1-\delta)u}{k_1 + u}][\frac{p^n}{k_2^n + p^n}] - \frac{\gamma u^d}{k_u^d + u^d} + \alpha, \tag{6}$$

$$\lambda \frac{dv}{dt} = \frac{k_3^m}{k_3^m + u^m} - v, \tag{7}$$

where w is a time-dependent inactivation variable, and $n = 3, d = m = 2$. Some typical values of the related parameters are $k = 3\mu M s^{-1}$ (M=Mol/L is the molar concentration), $k_1 = k_3 = 0.7\mu M, k_2 = 0.01\mu M, k_v = 1\mu M, k_u = 0.27\mu M, \delta = 0.11, \alpha = 0.15\mu M s^{-1}, \lambda = 0.2s$, $D_u = 20\mu m^2 s^{-1}, \gamma = 2\mu M s^{-1}$ [10].

By using the notation $s(u, v) = J_f - J_p + J_l$ and $g(u, v) = k_3^m/(k_3^m + u^m) - v$, we can obtain the steady state solution (u_0, v_0). From equations (1) and (2) together with equations (6) and (7), it is straightforward to check that they satisfy the Turing instability conditions

$$Q = \begin{pmatrix} s_u & s_v \\ g_u & g_v \end{pmatrix}, \tag{8}$$

which requires

$$\mathrm{tr}(Q) = s_u + g_v < 0, \;\; \mathrm{Det}(Q) = s_u g_v - f_v g_u > 0. \tag{9}$$

The model equations for intracellular calcium waves can be generally written in a system of reaction-diffusion equations in the form

$$\phi_t = D\nabla^2 \phi + f(\phi), \;\; \phi = [u \;\; v]^T, \tag{10}$$

where $D = \mathrm{diag}(D_u, 0)$. The rate $f(\phi)$ is a general nonlinear function coupling the different components u and v. This nonlinear reaction-diffusion system can be solved using conventional numerical method or stochastic cellular automata.

3 Stochastic Cellular Automaton

Conventionally, reaction-diffusion systems can be solved numerically using finite difference or finite element methods. Alternatively, the nonlinear systems can be simulated by using cellular automata [16]. The cellular automata for reaction-diffusion systems can be formulated to correspond to the solutions of the related partial differential equations in a qualitative manner [4] or quantitative manner [5]. The macroscopic approach via cellular automata as demonstrated by [16] is always more efficient than explicit numerical method and can be more efficient than better numerical technique in many cases.

The discretization of equation (10) can be written as

$$\frac{\phi_{i,j}^{n+1} - \phi_{i,j}^n}{\Delta t} = D[\frac{\phi_{i+1,j}^n - 2\phi_{i,j}^n + \phi_{i-1,j}^n}{(\Delta x)^2} + \frac{\phi_{i,j+1}^n - 2\phi_{i,j}^n + \phi_{i,j-1}^n}{(\Delta y)^2}] + f(\phi_{i,j}^n). \tag{11}$$

By taking $\Delta t = \Delta x = \Delta y = 1$, this becomes

$$\phi_{i,j}^{n+1} = D[(\phi_{i+1,j}^n + \phi_{i-1,j}^n + \phi_{i,j+1}^n + \phi_{i,j-1}^n) - 4\phi_{i,j}^n] + f(\phi_{i,j}^n), \tag{12}$$

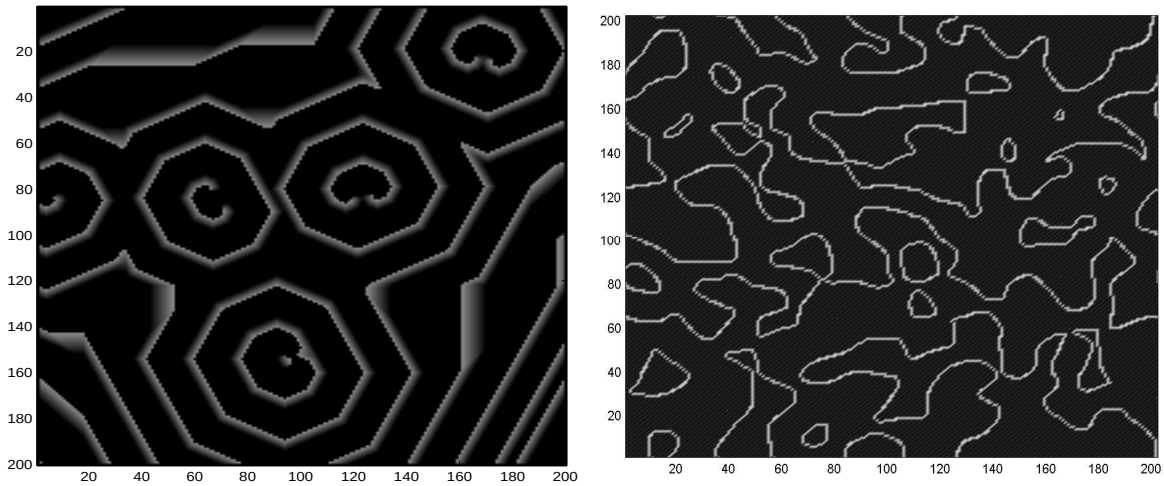

Figure 1: Pattern formation of calcium concentrations (spiral waves on the left and rings on the right) using values given in section 2.1

which can be written as a generic form

$$\phi_{i,j}^{n+1} = \sum_{k,l=-r}^{r} c_{k,l}\phi_{i+k,j+l}^{n} + f(\phi_{i,j}^{n}), \tag{13}$$

where the summation is over the $2r+1$ neighborhood. The coefficients c_k are determined from the discretization of the governing equations, and for this special case, $c_{-1,0} = c_{+1,0} = c_{0,-1} = c_{0,+1} = D, c_{0,0} = -4D$. In fact, this is equivalent to a finite-state cellular automaton with a transition rule $G = [g_{ij}]\ \ (i,j = 1,2,...,N)$ from one state $\Phi^n = [\phi_{ij}^n]\ \ (i,j = 1,2,...,N)$ at time level n to a new state $\Phi^{n+1} = [\phi_{ij}^{n+1}]\ \ (i,j = 1,2,...,N)$ at time level $n+1$. That is,

$$G : \Phi^n \mapsto \Phi^{n+1},\ \ g_{ij} : \phi_{ij}^n \mapsto \phi_{ij}^{n+1}. \tag{14}$$

The basic assumption for the rule inference for stochastic automata is that the function

$$g_{ij}(\phi_{ij}^n) = \phi_{ij}^{n+1},\ \ \mathcal{V} \le \Gamma(\phi_{ij}^n, f, r, N), \tag{15}$$

where Γ is a function with a range of $[0,1]$, and $\mathcal{V}$ is a random variable. At every time step, a random number $\mathcal{V}$ is generated for each automaton (i,j). The new state will only be updated if the generated random number is greater than Γ, otherwise, it remains unchanged. Following a similar derivation for ordinary differential equation [9], the probability function Γ can be written as

$$\Gamma(\phi_{ij}^n, f, r, N) = \Gamma(e^{-f}) = a + be^{-f}, \tag{16}$$

where a and b are coefficients depends on the number of finite states and other factors such as the accuracy of the approximation to the partial differential equations. The parameters of the continuum reaction-diffusion model shall be calibrated to fit the results given by the stochastic cellular automaton model using a least-squared procedure so as to get the related accurate transition rules.

4 Simulations and Results

By using the approach of stochastic cellular automata with finite number of states, we can now simulate the reaction-diffusion calcium transport and nonlinear calcium waves. Numerical simulations are carried out on an $N \times N$ lattice in 2-D setting, and usually, $N \ge 40$, or up to 1500. The number

of states is taken to be 256 in the present simulations. Different simulations with different lattice size are compared to ensure the simulated results are independent of the lattice size and time steps. In the rest of the paper, we present some results related to calcium pattern formation, nonlinear calcium waves and self-organized criticality of the complexity of reaction-diffusion systems.

4.1 Pattern Formation and Calcium Waves

From the initial random configuration, nonlinear reaction-diffusions can lead to complex patterns. Figure 1 shows two examples of the calcium concentrations evolving to the interesting patterns in 2-D configuration with 200×200 cells. The parameters used in the calculations are $k = 3\mu M s^{-1}$ (M=Mol/L is the molar concentration), $k_1 = k_3 = 0.7\mu M, k_2 = 0.01\mu M, k_v = 1\mu M, k_u = 0.27\mu M, \delta = 0.11, \alpha = 0.15\mu M s^{-1}, \lambda = 0.2s$. Spiral waves are formed for values $D_u = 5\mu m^2 s^{-1}$ (Fig 1a) while rings and ribbons are formed for higher value $D_u = 25\mu m^2 s^{-1}$ (Fig 1b). These patterns gradually evolve with time; however, the general characteristics of patterns only change slowly with time.

The simulations imply that patterns and structures formed by local transition rules are relatively stable. Our present results are consistent with the other well-known studies in pattern formation such as [11,12] for plants and sea shells by using nonlinear reaction-diffusion equations. In addition, our present simulations suggest that patterns arise naturally from the local interactions either through rule-based/agent-based evolution in terms of relationships among the neighbourhood individuals in stochastic cellular automata or partial differential equations in terms of system variables such as calcium concentrations. The initial configuration is not important. The rules of interactions or relationships between entities/individuals in the nearest neighbour are crucial factors that responsible for the behaviour of the system and pattern formations.

In addition, the spatial pattern formation of calcium concentration can provide some positional information of calcium distribution resulting from the reaction-diffusion transport among cells. This may have some important implication in the mechanism of calcium functionality in biological systems. Although many factors such as the function of proteins, genetic information and enzymes affect the intracellular transport of calcium, however, the calcium reaction-diffusion process itself could greatly contribute to the spatial distribution of calcium and thus be responsible to some extent for its positional information and signalling in biological systems. If it is the case, the modelling of calcium transport can be beneficial to the understanding of formation of the spatial structure and positional signalling coupled with the genetic and functional information in biological systems and physiological mechanisms.

The reaction-diffusion systems of calcium transport are complex. Nonlinear waves can arise under certain initial and boundary conditions. For a single source, the calcium concentration starts to expand and form nonlinear waves as shown in the figure on the left of Figure 2 which is a snapshot at $t = 500$. Numerical simulations imply that wave speed decreases with time as expect for any passive diffusion systems. In addition, the for a random configuration with periodic boundary conditions, complex nonlinear wave pattern have observed in numerical simulations as demonstrated in the figure on the right (Fig. 2b) where calcium concentration varies with space and time.

4.2 Complexity and Self-Organized Criticality

For a lattice $N = 100 \times 100$ with 256 states, the complexity of the cellular automata can be measured by its entropy S is defined as $S = -\sum_i p_i \log p_i$, where p_i is the probability of states i [1]. For a finite state automaton, p_i can be approximated by the calcium concentration so that

$$S = -\sum_i u_{ij} \log u_{ij}. \tag{17}$$

The variation of complexity or entropy of the stochastic cellular automata with time is shown in Figure 3a. It is clearly seen that the complexity varies significantly at the early stage of the pattern formation process, then it gradually relaxes to the equilibrium at long time, indicating that the reaction-diffusion system is in a quasi-steady state.

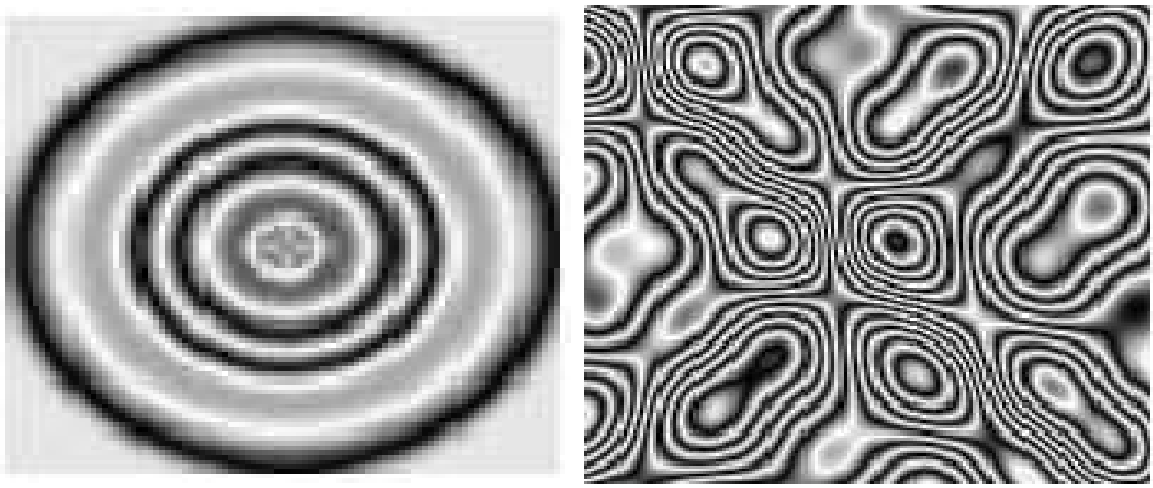

Figure 2: Nonlinear calcium waves for a single source (left) and multiple sources (right).

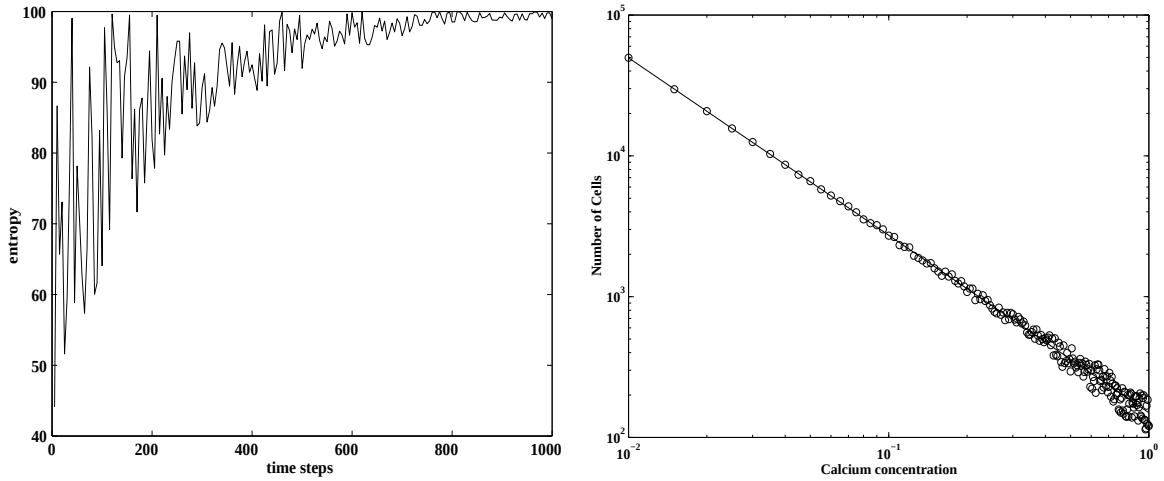

Figure 3: Complexity and entropy variations at different time steps (left). Self-organized criticality in calcium pattern formation leads to the exponent $\gamma = 1.26 \pm 0.02$ (right).

The complex pattern of calcium concentration can be measured by grouping or counting the number of cells for a given value of concentration. The results are plotted in Figure 3b. It is clearly seen that there exists a power law in the distribution of the number of cells (n) versus discrete calcium concentration (u). A least-square fitting of $n \propto u^{-\gamma}$, leads to the exponent of $\gamma = 1.26 \pm 0.02$. This implies the self-organized criticality in the complex calcium patterns.

This result may have important implications to the calcium transport mechanism. Although the detail of intracellular calcium oscillation and communication is not clear, it is likely that the intracellular and intracellular interactions mainly occur locally. Thus reaction-diffusion dominates the process without much contribution from the convection mechanism. This is consistent with the physiological aspects of calcium transport and functioning [4,10].

5 Conclusions

The finite state stochastic cellular automata have been formulated to simulate the reaction-diffusion systems of nonlinear calcium oscillations and waves using the transition rules derived from the partial

differential equations. By using the proper stochastic and transition rules between different states, the finite state automaton can simulate the complexity of calcium transport. Numerical experiments show that complex patterns can arise from the initial random configuration due to the local transition rules between entities of certain nearest neighborhood and the details of initial configuration is not important. The power-law relationship between number of cells and calcium concentrations implies self-organized criticality in the complex patterns.

6 References

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